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Prenatal exposure to environmental contaminants and behavioural problems at age 7–8 years

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ABSTRACT

Animal studies showed that the developing brain is particularly sensitive to chemical exposure. Human studies carried out in areas with high exposures have proven neurodevelopmental disorders in relation to e.g. lead and PCBs. Whether these chemicals are associated with behavioural problems in childhood at current environmental levels is not well known. Therefore, we assessed the association between prenatal exposure to lead, cadmium, PCBs, dioxin-like compounds, HCB and p,p′-DDE and behavioural problems in 7–8 year old children. Prenatal exposure data were obtained from the Flemish mother–new-born cohort. Lead, cadmium, PCBs, dioxin-like compounds, HCB and p,p′-DDE were analysed in cord blood. When the child reached 7–8 years, 270 mothers completed the Strengths and Difficulties Questionnaire assessing their children's behavioural health. We found that doubling the prenatal lead exposure (cord blood lead levels) was associated with a 3.43 times higher risk for hyperactivity in both boys and girls. In addition, total difficulties were 5.08 times more likely in the highest tertile for prenatal lead exposure compared to the lowest tertile. In girls, total difficulties were 4.92 more likely when doubling cord blood p,p′-DDE, whereas no significant association was found in boys. Further, we noted in boys a 1.53 times higher risk for emotional problems when doubling cord blood cadmium, whereas no significant association was found in girls. These results indicate that the presence of environmental contaminants influences the mental health of the next generation.

1. Introduction

Exposure to environmental contaminants remains an important concern in Western industrialized countries as well as in developing countries, since it influences the health of the current but also the future generations (Vermeir and Viaene, 2007). Not only new environmental contaminants (e.g. brominated or fluorinated compounds) but also some traditional persistent pollutants (heavy metals, organochlorinated pesticides) are still found in considerable amounts in the human body. Mounting evidence connects early-life exposure and later-life disease. Human exposure to adverse intrauterine environments – including environmental chemicals – can lead to increased disease risk later in life (Boekelheide et al., 2012). Cord blood can be non-invasively collected at birth and is an excellent matrix to monitor chemical exposures in new-borns. Contaminant concentrations in the cord blood represent the levels of chemicals that have passed through the blood–placenta barrier. In a Flemish Environment and Health Study (FLEHS I), lead (Pb), cadmium (Cd), polychlorinated biphenyls (PCBs), dioxin-like compounds, hexachlorobenze (HCB) and para,para-dichlorodiphenyldichloroethylene (p,p′-DDE) — a metabolite of dichlorodiphenyltrichloroethane (DDT) was measured in umbilical cord blood samples to assess the environmental contaminant load in Flemish children at the start of their lives (Koppen

Abbreviations: ADHD, attention deficit/hyperactivity disorder; AhR, aryl hydrocarbon receptor; BMI, body mass index; Cd, cadmium; DDT, dichlorodiphenyltrichloroethane; DF, dilution-factor; FLEHS, Flemish Environment and Health Study; GC-MS, gas chromatography with mass spectrometric detector; HCB, hexachlorobenzene; HR-ICP-MS, High Resolution Inductively Coupled Mass Spectrometry; IQR, interquartile range; LOD, limit of detection; LOQ, limit of quantification; OR, odds ratio; PCB, polychlorinated biphenyls; p,p′-DDE, para,para-dichlorodiphenyldichloroethylene; SDQ, strengths and difficulties questionnaire.

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et al., 2009; Schoeters et al., 2012). Four of these contaminants (lead, cadmium, PCBs and dioxin-like compounds) are proven ubiquitous developmental neurotoxins (Chiodo et al., 2004; Grandjean and Landrigan, 2006; Guo et al., 2004; Vermeir and Viaene, 2007; Viaene et al., 2000). Grandjean and Landrigan (2006) stated in their review that lead and PCBs are recognized causes of neurodevelopmental disorders and subclinical brain dysfunction. Exposure to these chemicals during early foetal development can cause brain injury at doses much lower than those affecting adult brain function (Grandjean and Landrigan, 2006). Patandin et al. (1999) and Vreugdenhil et al. (2002) found an inverse relation between maternal PCB concentrations and cognitive performance in Dutch children at 42 months and 7.5 years of age, respectively. In addition, prenatal as well as postnatal environmental exposures to heavy metals, especially lead may result in behavioural changes and intellectual deficits in young children as well as in adolescents (Al-Saleh et al., 2009; Bellinger et al., 1994; Eubig et al., 2010; Marcus et al., 2010; Vermeir et al., 2005; Viaene et al., 2000).

Here we test the hypothesis that prenatal exposure to low levels of some traditional persistent contaminants (Pb, Cd, PCBs, dioxin-like compounds, HCB and p,p′-DDE) negatively influences behavioural aspects (emotional, conduct, hyperactivity, peer and prosocial problems) of the children when being 7 to 8 years old; e.g. whether prenatal lead exposure increased the risk on hyperactivity problems. Behavioural problems were measured using the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997), which allows assessment of a broad range of behavioural problems. This instrument was previously used to assess whether prenatal exposure to perfluorinated chemicals or to tobacco was associated with behavioural problems (Fei and Olsen, 2011; Ruckinger et al., 2010).

2. Material and methods

2.1. Study design and study population

The study population is recruited within the mother and new-born cohort of the first Flemish Environment and Health Study (FLEHS I, 2002–2006) (Schoeters et al., 2012). Within FLEHS I, 1196 mothers and their new-borns were recruited by a stratified clustered multistage design, i.e. through 25 maternity hospitals between October 2002 and December 2003. These hospitals were spread over eight different areas with characteristic environmental exposures. Inclusion criteria were living for at least five years in the area of interest and being able to fill out Dutch questionnaires. Cord blood was sampled at the moment of the delivery and six traditional contaminants were measured: (1) lead and cadmium in blood and (2) PCBs, dioxin-like compounds (total concentration of PCDD/Fs and dioxin-like PCBs), HCB and p,p′-DDE in plasma. More information about the study design of FLEHS I is described by Koppen et al. (2009).

In the summer of 2011, the parents of the children that participated as new-borns in 2002–2003 were re-contacted to participate in a follow-up study in order to evaluate the impact of the prenatal exposure to the six contaminants – as measured in FLEHS I – on the health of the children when they were 7 to 8 years old. The parents and children received an invitation letter explaining the aims of the follow-up study, as well as an informed consent and a postal questionnaire.

In total, 1173 invitation letters for the follow-up study were sent in June 2011, since 23 of the 1196 parents had indicated at the baseline study in 2002–2003 that they were not willing to participate in follow-up studies. However, 109 closed envelops came back, because the participants had moved between 2002 and 2011. In total, 281 completed questionnaires came back, leading to a response rate of 26.4%. All participating parents provided written informed consent for participation. The study protocol was approved by the Ethical Committee of the University of Antwerp (Belgium) and the Ghent University (Belgium).

2.2. Prenatal exposure

Cord blood was aliquoted and plasma was separated by centrifugation within one day in either the maternity or blood bank laboratories. The aliquoted samples were kept in the refrigerator for maximal one week. Since we only measured persistent chemicals (lead, cadmium, persistent chlorinated compounds) that do not degrade, this method is in line with quality standards. Afterwards they were put at −20 °C until analysis. In cord plasma, marker polychlorinated biphenyls (PCB 138, 153 and 180), PCB 118 and 170, dioxin-like compounds (total of PCDD/Fs and dioxin-like PCBs) and chlorinated pesticides (HCB and p, p′-DDE) were analysed. The PCBs and chlorinated pesticides were analysed by gas chromatography with mass spectrometric detector (GC-MS) using the method of Gomara et al. (2002). The limit of detection (LOD) for all chlorinated compounds was 0.02 μg/L. Routinely measured cholesterol and triglycerides were used to express the results on a lipid weight basis (Covaci et al., 2006). Exposure to dioxin-like compounds was assessed via the CALUX® assay, based on in vitro activation of the aryl hydrocarbon receptor (AhR) of cultured H4IIE rat hepatoma cells by the dioxin-like compounds present in 5 mL cord plasma (BioDetection Systems BV, Amsterdam, The Netherlands). The extraction and clean-up procedures were performed as described in Koppen et al. (2001). The limit of detection was 0.03 pg CALUX-TEQ/mL or 14 pg CALUX-TEQ/g lipids for 5 mL plasma, with a lipid content of 200 mg/dL (Koppen et al., 2009). Prenatal PCB, dioxin and p,p′-DDE concentration was available for 256, 200 and 259 children, respectively; none of the concentrations were below LOD. Prenatal HCB concentration was available for 248 children; for 60 cases (24.2%) the concentration was below LOD and replaced by LOD/2.

In cord blood, lead and cadmium were analysed using High Resolution Inductively Coupled Mass Spectrometry (HR-ICP-MS). For more information see Schroijen et al. (2008). The LOD for lead and cadmium in whole blood samples were 0.09 and 2.0 μg/L, respectively. Prenatal cadmium exposure data was available for 257 children; in 94 cases (36.6%) the concentration was below LOD and replaced by LOD/2. Prenatal lead exposure data was also available for 257 children; in 13 cases (5.1%) the concentration was below LOD and replaced by LOD/2.

2.3. Outcome measure

We assessed behavioural problems using the standardized Strengths and Difficulties Questionnaire (SDQ; www.sdqinfo.com). This SDQ is an internationally applied and validated screening questionnaire, which compromises five domains: emotional, conduct, hyperactivity, peer and social problems (Goodman, 1997; Goodman et al., 1998). The parents completed a list of 25 statements that reflected their children's behaviour in the previous six months. For each of the 25 statements, parents could give three possible answers: 'not true' (0), 'somewhat true' (1) and 'certainly true' (2). Subscale scores were computed by summing scores on five items belonging to that subscale, giving a range from 0 to 10. Higher scores on the 'prosocial behaviour subscale' reflected strengths, whereas higher scores on the other four subscales reflected difficulties. The scores of these four scales (emotional, conduct, hyperactivity and peer problems) were further summed to generate a total difficulties score ranging from 0 to 40. In the present study – as no cut-off points based on a Belgian sample were available – the German cut-off points were used to classify children as "normal", "borderline" or "abnormal" on each scale and on the total difficulties score. These cut-off points were established in a representative sample of German children in order to classify about 10% of the children as borderline and 10% of the children as abnormal (Woerner et al., 2004).

2.4. General questionnaire

Besides the SDQ questionnaire, the parents also completed a general questionnaire to collect information on possible confounders and